Clinical trial results:
An Open-label Phase 2 Multi-cohort Trial of Nivolumab in Advanced or Metastatic Malignancies (CheckMate 627: CHECKpoint pathway and nivoluMAb clinical Trial Evaluation 627)

Summary

EudraCT number	2016-000461-23
Trial protocol	DE
Global end of trial date	24 June 2021

Results information

Result version number	v1 (current)
This version publication date	22 April 2022
First version publication date	22 April 2022

Trial information

Trial identification

Sponsor protocol code	CA209-627

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Bristol-Myers Squibb
Sponsor organisation address	Chaussée de la Hulpe 185, Brussels, Belgium, 1170
Public contact	EU Study Start-Up Unit, Bristol-Myers Squibb International Corporation, Clinical.Trials@bms.com
Scientific contact	Bristol-Myers Squibb Study Director, Bristol-Myers Squibb, Clinical.Trials@bms.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	20 August 2021
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	24 June 2021
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the investigator-assessed ORR of nivolumab monotherapy in advanced or metastatic malignancies

Protection of trial subjects:

The study was in compliance with the ethical principles derived from the Declaration of Helsinki and in compliance with all International Conference on Harmonization Good Clinical Practice Guidelines. All the local regulatory requirements pertinent to safety of trial participants were followed.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	22 February 2016
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Germany: 65
Country: Number of subjects enrolled	United States: 174
Worldwide total number of subjects	239
EEA total number of subjects	65

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	152
From 65 to 84 years	84
85 years and over	3

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

239 participants were treated.

Period 1

Period 1 title	Treatment Period 1
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Advanced Malignancies Cohort

Arm description:

Treatment period 1: Nivolumab 240 mg Q2W for 8 doses. Treatment period 2: Nivolumab 480 mg Q4W

Arm type	Experimental
Investigational medicinal product name	BMS-936558
Investigational medicinal product code	
Other name	Nivolumab
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

240 mg Q2W for 8 doses

Number of subjects in period 1	Advanced Malignancies Cohort
Started	239
Completed	110
Not completed	129
Adverse event, serious fatal	2
No longer meet study criteria	1
Disease progression	90
Participant withdrew consent	3
Participant request to discontinue	9
Adverse event unrelated to study drug	12
Other reasons	6
Study Drug Toxicity	6

Period 2

Period 2 title	Treatment Period 2
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Advanced Malignancies Cohort

Arm description:

Treatment period 1: Nivolumab 240 mg Q2W for 8 doses. Treatment period 2: Nivolumab 480 mg Q4W

Arm type	Experimental
Investigational medicinal product name	BMS-936558
Investigational medicinal product code	
Other name	Nivolumab
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

480 mg Q4W up to 24 months of total treatment (Treatment Period 1 + Treatment Period 2)

Number of subjects in period 2[1]	Advanced Malignancies Cohort
Started	103
Completed	19
Not completed	84
Disease progression	69
Participant withdrew consent	3
Maximum clinical benefit	1
Participant request to discontinue	2
Adverse event unrelated to study drug	1
Other reasons	3
Study Drug Toxicity	5

Notes:

[1] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.
Justification: Not all the participants who completed Treatment Period 1 continued in Treatment Period 2

Baseline characteristics

Reporting groups	
Reporting group title	Advanced Malignancies Cohort
Reporting group description:	
Treatment period 1: Nivolumab 240 mg Q2W for 8 doses. Treatment period 2: Nivolumab 480 mg Q4W	

Reporting group values	Advanced Malignancies Cohort	Total	
Number of subjects	239	239	
Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	152	152	
From 65-84 years	84	84	
85 years and over	3	3	
Age Continuous Units: Years			
arithmetic mean	59.2		
standard deviation	± 13.79	-	
Sex: Female, Male Units: Participants			
Female	148	148	
Male	91	91	
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	0	0	
Asian	9	9	
Native Hawaiian or Other Pacific Islander	0	0	
Black or African American	20	20	
White	203	203	
More than one race	0	0	
Unknown or Not Reported	7	7	
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	11	11	
Not Hispanic or Latino	158	158	
Unknown or Not Reported	70	70	

End points

End points reporting groups

Reporting group title	Advanced Malignancies Cohort
Reporting group description:	
Treatment period 1: Nivolumab 240 mg Q2W for 8 doses. Treatment period 2: Nivolumab 480 mg Q4W	
Reporting group title	Advanced Malignancies Cohort
Reporting group description:	
Treatment period 1: Nivolumab 240 mg Q2W for 8 doses. Treatment period 2: Nivolumab 480 mg Q4W	

Primary: Objective Response Rate (ORR)

End point title	Objective Response Rate (ORR)[1]

End point description:

ORR is defined as the percentage of participants with a best overall response (BOR) of confirmed Complete Response (CR) or Partial Response (PR). Best overall response is defined as the best response designation, as determined by investigator, recorded in the specified timeframe, according to the RECIST 1.1 criteria.

End point type	Primary

End point timeframe:

From first dose to the date of objectively documented progression (per tumor-specific response criteria) or the date of subsequent therapy, whichever occurs first (up to approximately 24 months)

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No statistical analyses were performed for this endpoint

End point values	Advanced Malignancies Cohort			
Subject group type	Reporting group			
Number of subjects analysed	239			
Units: Percent of Participants				
number (confidence interval 95%)	7.9 (4.9 to 12.1)			

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Response (DOR)

End point title	Duration of Response (DOR)

End point description:

DOR is defined as the time from first confirmed response (Complete Response, CR or Partial Response, PR) to the date of the first documented tumor progression (as determined by investigator) or death due to any cause, whichever occurs first. Median DOR computed using Kaplan-Meier method

End point type	Secondary

End point timeframe:

From the time of first confirmed response to the date of the first documented progression (up to approximately 22 months)

End point values	Advanced Malignancies Cohort			
Subject group type	Reporting group			
Number of subjects analysed	19			
Units: Months				
median (full range (min-max))	21.78 (2.8 to 22.3)			

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Objective Response (TTR)

End point title	Time to Objective Response (TTR)

End point description:

TTR is defined as the time from first dosing date to the date of the first confirmed response (Complete Response, CR or Partial Response, PR), as assessed by investigator.

End point type	Secondary

End point timeframe:

From the first dosing date to the date of the first confirmed response (up to approximately 10 months)

End point values	Advanced Malignancies Cohort			
Subject group type	Reporting group			
Number of subjects analysed	19			
Units: Months				
arithmetic mean (standard deviation)	3.54 (± 2.337)			

Statistical analyses

No statistical analyses for this end point

Secondary: Clinical Benefit Rate (CBR)

End point title	Clinical Benefit Rate (CBR)

End point description:

CBR is defined as the percentage of participants with a best overall response of confirmed Complete Response (CR) or Partial Response (PR) or Stable Disease (SD).

End point type	Secondary

End point timeframe:

From the first dosing date to the date of the last dose (approximately 24 months)

End point values	Advanced Malignancies Cohort			
Subject group type	Reporting group			
Number of subjects analysed	239			
Units: Percent of participants				
number (confidence interval 95%)	49.8 (43.3 to 56.3)			

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival Rate at 1 Year

End point title	Overall Survival Rate at 1 Year

End point description:

Overall Survival (OS) is defined as the time from the first dosing date to the date of death. A participant who has not died will be censored at last known date alive. OS rate at 1 year is measured as the percent of participants still alive at 1 year after first dosing, measured from Kaplan-Meier curve of OS.

End point type	Secondary

End point timeframe:

From the first dosing date to 1 year later

End point values	Advanced Malignancies Cohort			
Subject group type	Reporting group			
Number of subjects analysed	239			
Units: Percent of participants				
number (confidence interval 95%)	56.1 (49.1 to 62.5)			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants Who Died

End point title	Number of Participants Who Died

End point description:

Number of participants who died for any cause

End point type	Secondary

End point timeframe:

From first dose to 100 days following last dose (up approximately 27 months)

End point values	Advanced Malignancies Cohort			
Subject group type	Reporting group			
Number of subjects analysed	239			
Units: Participants	72			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants Experiencing Adverse Events (AEs)

End point title	Number of Participants Experiencing Adverse Events (AEs)

End point description:

Number of participants who experienced any grade, any cause AEs

End point type	Secondary

End point timeframe:

From first dose to 30 days following the last dose (up to approximately 25 months)

End point values	Advanced Malignancies Cohort			
Subject group type	Reporting group			
Number of subjects analysed	239			
Units: Participants	234			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants Experiencing Serious Adverse Events (SAEs)

End point title	Number of Participants Experiencing Serious Adverse Events (SAEs)

End point description:

Number of participants who experienced any grade, any cause SAEs

End point type	Secondary

End point timeframe:

From first dose to 100 days following the last dose (up to approximately 27 months)

End point values	Advanced Malignancies Cohort			
Subject group type	Reporting group			
Number of subjects analysed	239			
Units: Participants	148			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants Experiencing Adverse Events (AEs) Leading to Discontinuation

End point title	Number of Participants Experiencing Adverse Events (AEs) Leading to Discontinuation

End point description:

Number of participants who experienced AEs leading to discontinuation of study therapy

End point type	Secondary

End point timeframe:

From first dose to 30 days following the last dose (up to approximately 25 months)

End point values	Advanced Malignancies Cohort			
Subject group type	Reporting group			
Number of subjects analysed	239			
Units: Participants	41			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants Experiencing Immune-mediated Adverse Events (IMAEs)

End point title	Number of Participants Experiencing Immune-mediated Adverse Events (IMAEs)

End point description:

Number of participants who experienced IMAEs. IMAEs are AEs consistent with an immune-mediated mechanism or immune-mediated component for which non-inflammatory etiologies (eg, infection or tumor progression) have been ruled out. IMAEs can include events with an alternate etiology which were exacerbated by the induction of autoimmunity.

End point type	Secondary

End point timeframe:

From first dose to 100 days following the last dose (up to approximately 27 months)

End point values	Advanced Malignancies Cohort			
Subject group type	Reporting group			
Number of subjects analysed	239			
Units: Participants	8			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants Experiencing Select Adverse Events

End point title	Number of Participants Experiencing Select Adverse Events

End point description:

Number of participants who experienced Select Adverse Events. Select Adverse Events categories include: gastrointestinal, hepatic, pulmonary, renal, skin, hypersensitivity/infusion reaction.

End point type	Secondary

End point timeframe:

From first dose to 30 days following the last dose (up to approximately 25 months)

End point values	Advanced Malignancies Cohort			
Subject group type	Reporting group			
Number of subjects analysed	239			
Units: Participants				
Gastrointestinal Select AEs	57			
Hepatic Select AEs	33			
Pulmonary Select AEs	6			
Renal Select AEs	22			
Skin Select AEs	59			
Hypersensitivity/Infusion Reaction	7			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants Experiencing Adverse Events (AEs) Leading to Dose Delay or Dose Reduction

End point title	Number of Participants Experiencing Adverse Events (AEs)

	Leading to Dose Delay or Dose Reduction

End point description:

Number of participants who experienced AEs leading to dose delay or dose reduction. A dose will be considered as delayed if the delay is exceeding 3 days after the intended dose date (i.e., greater than or equal to 4 days from scheduled dosing date)

End point type	Secondary

End point timeframe:

From first dose to 30 days following the last dose (up to approximately 25 months)

End point values	Advanced Malignancies Cohort			
Subject group type	Reporting group			
Number of subjects analysed	239			
Units: Participants	61			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants Experiencing Laboratory Abnormalities in Specific Liver Tests

End point title	Number of Participants Experiencing Laboratory Abnormalities in Specific Liver Tests

End point description:

Number of participants who experienced the laboratory abnormalities in specific liver tests described in the individual categories. ALT = Alanine Aminotransferase AST = Aspartate Aminotransferase ULN = Upper Limit of Normal

End point type	Secondary

End point timeframe:

From first dose to 30 days following the last dose (up to approximately 25 months)

End point values	Advanced Malignancies Cohort			
Subject group type	Reporting group			
Number of subjects analysed	231			
Units: Participants				
ALT OR AST > 3XULN	11			
ALT OR AST > 5XULN	8			
ALT OR AST > 10XULN	3			
ALT OR AST > 20XULN	1			
TOTAL BILIRUBIN > 2XULN	5			
ALT/AST > 3XULN + BILIR > 2XULN 1 DAY	3			
ALT/AST > 3XULN + BILIR > 2XULN 30 DAYS	3			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants Experiencing Laboratory Abnormalities in Specific Thyroid Tests

End point title	Number of Participants Experiencing Laboratory Abnormalities in Specific Thyroid Tests

End point description:

Number of participants who experienced the laboratory abnormalities in specific thyroid tests described in the individual categories. TSH = Thyroid Stimulating Hormone LLN = Lower Limit of Normal ULN = Upper Limit of Normal

End point type	Secondary

End point timeframe:

From first dose to 100 days following the last dose (up to approximately 27 months)

End point values	Advanced Malignancies Cohort			
Subject group type	Reporting group			
Number of subjects analysed	238			
Units: Participants				
TSH > ULN	62			
TSH > ULN WITH TSH <= ULN AT BASELINE	42			
TSH > ULN WITH AT LEAST 1 FT3/FT4 TEST VALUE < LLN	12			
TSH > ULN WITH ALL FT3/FT4 TEST VALUE >= LLN	0			
TSH > ULN WITH FT3/FT4 MISSING	2			
TSH < LLN	38			
TSH < LLN WITH TSH >= LLN AT BASELINE	25			
TSH < LLN WITH AT LEAST 1 FT3/FT4 TEST VALUE > ULN	8			
TSH < LLN WITH ALL FT3/FT4 TEST VALUES <= ULN	1			
TSH < LLN WITH FT3/FT4 TEST MISSING	1			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

All-cause mortality was assessed from first dose to study completion date (approximately 64 months). SAEs and Other AEs were assessed from first dose to 100 days following administration of the last dose (approximately 27 months).

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	24.0

Reporting groups

Reporting group title	Advanced Malignancies Cohort

Reporting group description:

Treatment period 1: Nivolumab 240 mg Q2W for 8 doses. Treatment period 2: Nivolumab 480 mg Q4W

Serious adverse events	Advanced Malignancies Cohort		
Total subjects affected by serious adverse events			
subjects affected / exposed	148 / 239 (61.92%)		
number of deaths (all causes)	156		
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Infected neoplasm			
subjects affected / exposed	1 / 239 (0.42%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Brain neoplasm			
subjects affected / exposed	1 / 239 (0.42%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Adenoid cystic carcinoma			
subjects affected / exposed	1 / 239 (0.42%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Malignant neoplasm of cornea			

subjects affected / exposed	1 / 239 (0.42%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Malignant neoplasm progression				
subjects affected / exposed	58 / 239 (24.27%)			
occurrences causally related to treatment / all	0 / 59			
deaths causally related to treatment / all	0 / 52			
Mesothelioma				
subjects affected / exposed	2 / 239 (0.84%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 2			
Tumour haemorrhage				
subjects affected / exposed	1 / 239 (0.42%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Tumour pain				
subjects affected / exposed	4 / 239 (1.67%)			
occurrences causally related to treatment / all	0 / 4			
deaths causally related to treatment / all	0 / 0			
Squamous cell carcinoma				
subjects affected / exposed	1 / 239 (0.42%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Penis carcinoma metastatic				
subjects affected / exposed	1 / 239 (0.42%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Neoplasm progression				
subjects affected / exposed	2 / 239 (0.84%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 2			
Transitional cell carcinoma				

subjects affected / exposed	1 / 239 (0.42%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
Embolism			
subjects affected / exposed	1 / 239 (0.42%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Venous stenosis			
subjects affected / exposed	1 / 239 (0.42%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
General physical health deterioration			
subjects affected / exposed	4 / 239 (1.67%)		
occurrences causally related to treatment / all	0 / 5		
deaths causally related to treatment / all	0 / 0		
Fatigue			
subjects affected / exposed	1 / 239 (0.42%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Asthenia			
subjects affected / exposed	2 / 239 (0.84%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Pain			
subjects affected / exposed	1 / 239 (0.42%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Non-cardiac chest pain			
subjects affected / exposed	1 / 239 (0.42%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Localised oedema				
subjects affected / exposed	1 / 239 (0.42%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Peripheral swelling				
subjects affected / exposed	1 / 239 (0.42%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Sudden death				
subjects affected / exposed	1 / 239 (0.42%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Pyrexia				
subjects affected / exposed	2 / 239 (0.84%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Immune system disorders				
Anaphylactic reaction				
subjects affected / exposed	1 / 239 (0.42%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Reproductive system and breast disorders				
Vaginal haemorrhage				
subjects affected / exposed	2 / 239 (0.84%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 0			
Vulvovaginal pain				
subjects affected / exposed	1 / 239 (0.42%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Respiratory, thoracic and mediastinal disorders				
Acute respiratory failure				

subjects affected / exposed	3 / 239 (1.26%)			
occurrences causally related to treatment / all	0 / 4			
deaths causally related to treatment / all	0 / 0			
Bronchostenosis				
subjects affected / exposed	1 / 239 (0.42%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pleural effusion				
subjects affected / exposed	4 / 239 (1.67%)			
occurrences causally related to treatment / all	0 / 4			
deaths causally related to treatment / all	0 / 0			
Pneumothorax				
subjects affected / exposed	1 / 239 (0.42%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Laryngeal haemorrhage				
subjects affected / exposed	1 / 239 (0.42%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Hypoxia				
subjects affected / exposed	1 / 239 (0.42%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Dyspnoea				
subjects affected / exposed	5 / 239 (2.09%)			
occurrences causally related to treatment / all	0 / 6			
deaths causally related to treatment / all	0 / 1			
Pulmonary embolism				
subjects affected / exposed	1 / 239 (0.42%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pulmonary hypertension				

subjects affected / exposed	1 / 239 (0.42%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Respiratory failure			
subjects affected / exposed	1 / 239 (0.42%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Psychiatric disorders			
Mental status changes			
subjects affected / exposed	1 / 239 (0.42%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Delirium			
subjects affected / exposed	1 / 239 (0.42%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Investigations			
Transaminases increased			
subjects affected / exposed	1 / 239 (0.42%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
C-reactive protein increased			
subjects affected / exposed	1 / 239 (0.42%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Blood creatinine increased			
subjects affected / exposed	2 / 239 (0.84%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Humerus fracture			
subjects affected / exposed	1 / 239 (0.42%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Post procedural fever				
subjects affected / exposed	1 / 239 (0.42%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Cardiac disorders				
Acute myocardial infarction				
subjects affected / exposed	1 / 239 (0.42%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Cardiac arrest				
subjects affected / exposed	1 / 239 (0.42%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Cardiac failure congestive				
subjects affected / exposed	1 / 239 (0.42%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 1			
Cardio-respiratory arrest				
subjects affected / exposed	1 / 239 (0.42%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Myocardial infarction				
subjects affected / exposed	2 / 239 (0.84%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 1			
Supraventricular tachycardia				
subjects affected / exposed	1 / 239 (0.42%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Ventricular tachycardia				
subjects affected / exposed	1 / 239 (0.42%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Nervous system disorders				

Brain oedema				
subjects affected / exposed	1 / 239 (0.42%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Cerebellar infarction				
subjects affected / exposed	1 / 239 (0.42%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Spinal cord compression				
subjects affected / exposed	1 / 239 (0.42%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Neuritis cranial				
subjects affected / exposed	1 / 239 (0.42%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Intracranial mass				
subjects affected / exposed	1 / 239 (0.42%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Headache				
subjects affected / exposed	1 / 239 (0.42%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Facial paralysis				
subjects affected / exposed	1 / 239 (0.42%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Cerebrovascular accident				
subjects affected / exposed	2 / 239 (0.84%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Cerebral infarction				

subjects affected / exposed	1 / 239 (0.42%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	3 / 239 (1.26%)		
occurrences causally related to treatment / all	0 / 4		
deaths causally related to treatment / all	0 / 0		
Eye disorders			
Eye swelling			
subjects affected / exposed	1 / 239 (0.42%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Eye pain			
subjects affected / exposed	1 / 239 (0.42%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	9 / 239 (3.77%)		
occurrences causally related to treatment / all	0 / 12		
deaths causally related to treatment / all	0 / 0		
Diarrhoea			
subjects affected / exposed	5 / 239 (2.09%)		
occurrences causally related to treatment / all	2 / 5		
deaths causally related to treatment / all	0 / 0		
Colitis			
subjects affected / exposed	4 / 239 (1.67%)		
occurrences causally related to treatment / all	4 / 4		
deaths causally related to treatment / all	0 / 0		
Abdominal pain upper			
subjects affected / exposed	2 / 239 (0.84%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		

Abdominal pain lower				
subjects affected / exposed	1 / 239 (0.42%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Diverticulum intestinal haemorrhagic				
subjects affected / exposed	1 / 239 (0.42%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Dysphagia				
subjects affected / exposed	1 / 239 (0.42%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Gastric haemorrhage				
subjects affected / exposed	1 / 239 (0.42%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Gastrointestinal haemorrhage				
subjects affected / exposed	1 / 239 (0.42%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Lower gastrointestinal haemorrhage				
subjects affected / exposed	1 / 239 (0.42%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Inguinal hernia				
subjects affected / exposed	1 / 239 (0.42%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Ileus				
subjects affected / exposed	2 / 239 (0.84%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Gastrointestinal oedema				

subjects affected / exposed	1 / 239 (0.42%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Intestinal obstruction				
subjects affected / exposed	1 / 239 (0.42%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Subileus				
subjects affected / exposed	2 / 239 (0.84%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Small intestinal obstruction				
subjects affected / exposed	6 / 239 (2.51%)			
occurrences causally related to treatment / all	1 / 7			
deaths causally related to treatment / all	0 / 1			
Proctalgia				
subjects affected / exposed	1 / 239 (0.42%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Nausea				
subjects affected / exposed	4 / 239 (1.67%)			
occurrences causally related to treatment / all	2 / 4			
deaths causally related to treatment / all	0 / 0			
Vomiting				
subjects affected / exposed	4 / 239 (1.67%)			
occurrences causally related to treatment / all	1 / 4			
deaths causally related to treatment / all	0 / 0			
Hepatobiliary disorders				
Cholecystitis				
subjects affected / exposed	3 / 239 (1.26%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 0			
Hepatic lesion				

subjects affected / exposed	1 / 239 (0.42%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Skin and subcutaneous tissue disorders			
Rash maculo-papular			
subjects affected / exposed	1 / 239 (0.42%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	4 / 239 (1.67%)		
occurrences causally related to treatment / all	0 / 4		
deaths causally related to treatment / all	0 / 1		
Chronic kidney disease			
subjects affected / exposed	1 / 239 (0.42%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hydronephrosis			
subjects affected / exposed	1 / 239 (0.42%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Renal failure			
subjects affected / exposed	2 / 239 (0.84%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 1		
Urinary tract obstruction			
subjects affected / exposed	2 / 239 (0.84%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Haematuria			
subjects affected / exposed	1 / 239 (0.42%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Endocrine disorders			

Hypophysitis			
subjects affected / exposed	1 / 239 (0.42%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Hyperthyroidism			
subjects affected / exposed	1 / 239 (0.42%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Flank pain			
subjects affected / exposed	1 / 239 (0.42%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Back pain			
subjects affected / exposed	3 / 239 (1.26%)		
occurrences causally related to treatment / all	0 / 5		
deaths causally related to treatment / all	0 / 0		
Arthralgia			
subjects affected / exposed	2 / 239 (0.84%)		
occurrences causally related to treatment / all	2 / 3		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal chest pain			
subjects affected / exposed	1 / 239 (0.42%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Neck pain			
subjects affected / exposed	1 / 239 (0.42%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Myositis			
subjects affected / exposed	1 / 239 (0.42%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	1 / 1		

Infections and infestations			
Bacteraemia			
subjects affected / exposed	1 / 239 (0.42%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cholecystitis infective			
subjects affected / exposed	1 / 239 (0.42%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cellulitis			
subjects affected / exposed	3 / 239 (1.26%)		
occurrences causally related to treatment / all	0 / 5		
deaths causally related to treatment / all	0 / 0		
Bronchitis			
subjects affected / exposed	1 / 239 (0.42%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Device related infection			
subjects affected / exposed	1 / 239 (0.42%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Febrile infection			
subjects affected / exposed	1 / 239 (0.42%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Erysipelas			
subjects affected / exposed	1 / 239 (0.42%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Enterocolitis infectious			
subjects affected / exposed	1 / 239 (0.42%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Diverticulitis			

subjects affected / exposed	2 / 239 (0.84%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Diarrhoea infectious				
subjects affected / exposed	1 / 239 (0.42%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Fungaemia				
subjects affected / exposed	1 / 239 (0.42%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Gastroenteritis				
subjects affected / exposed	1 / 239 (0.42%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Herpes zoster				
subjects affected / exposed	2 / 239 (0.84%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Pelvic abscess				
subjects affected / exposed	1 / 239 (0.42%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Pneumonia				
subjects affected / exposed	7 / 239 (2.93%)			
occurrences causally related to treatment / all	0 / 8			
deaths causally related to treatment / all	0 / 0			
Pharyngitis streptococcal				
subjects affected / exposed	1 / 239 (0.42%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Intervertebral discitis				

subjects affected / exposed	1 / 239 (0.42%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Infectious pleural effusion				
subjects affected / exposed	2 / 239 (0.84%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Perinephric abscess				
subjects affected / exposed	1 / 239 (0.42%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Renal abscess				
subjects affected / exposed	1 / 239 (0.42%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Sepsis				
subjects affected / exposed	8 / 239 (3.35%)			
occurrences causally related to treatment / all	0 / 10			
deaths causally related to treatment / all	0 / 3			
Septic shock				
subjects affected / exposed	2 / 239 (0.84%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Skin infection				
subjects affected / exposed	1 / 239 (0.42%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Urinary tract infection				
subjects affected / exposed	3 / 239 (1.26%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 0			
Urosepsis				

subjects affected / exposed	1 / 239 (0.42%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	1 / 239 (0.42%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hypovolaemia			
subjects affected / exposed	1 / 239 (0.42%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Diabetes mellitus			
subjects affected / exposed	1 / 239 (0.42%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Hypokalaemia			
subjects affected / exposed	1 / 239 (0.42%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hypomagnesaemia			
subjects affected / exposed	1 / 239 (0.42%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Dehydration			
subjects affected / exposed	5 / 239 (2.09%)		
occurrences causally related to treatment / all	2 / 5		
deaths causally related to treatment / all	0 / 0		
Lactic acidosis			
subjects affected / exposed	1 / 239 (0.42%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Advanced Malignancies Cohort		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	216 / 239 (90.38%)		
Vascular disorders			
Hypertension			
subjects affected / exposed	17 / 239 (7.11%)		
occurrences (all)	17		
General disorders and administration site conditions			
Chills			
subjects affected / exposed	14 / 239 (5.86%)		
occurrences (all)	16		
Fatigue			
subjects affected / exposed	90 / 239 (37.66%)		
occurrences (all)	102		
Oedema peripheral			
subjects affected / exposed	24 / 239 (10.04%)		
occurrences (all)	25		
Pyrexia			
subjects affected / exposed	24 / 239 (10.04%)		
occurrences (all)	29		
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	43 / 239 (17.99%)		
occurrences (all)	53		
Dyspnoea			
subjects affected / exposed	44 / 239 (18.41%)		
occurrences (all)	51		
Psychiatric disorders			
Insomnia			
subjects affected / exposed	18 / 239 (7.53%)		
occurrences (all)	18		
Anxiety			

subjects affected / exposed	13 / 239 (5.44%)		
occurrences (all)	13		
Investigations			
Blood alkaline phosphatase increased			
subjects affected / exposed	12 / 239 (5.02%)		
occurrences (all)	12		
Aspartate aminotransferase increased			
subjects affected / exposed	18 / 239 (7.53%)		
occurrences (all)	19		
Alanine aminotransferase increased			
subjects affected / exposed	16 / 239 (6.69%)		
occurrences (all)	19		
Blood creatinine increased			
subjects affected / exposed	15 / 239 (6.28%)		
occurrences (all)	15		
Weight decreased			
subjects affected / exposed	22 / 239 (9.21%)		
occurrences (all)	23		
Nervous system disorders			
Headache			
subjects affected / exposed	19 / 239 (7.95%)		
occurrences (all)	21		
Dizziness			
subjects affected / exposed	15 / 239 (6.28%)		
occurrences (all)	15		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	41 / 239 (17.15%)		
occurrences (all)	42		
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	33 / 239 (13.81%)		
occurrences (all)	35		
Abdominal pain upper			
subjects affected / exposed	12 / 239 (5.02%)		
occurrences (all)	12		

Vomiting subjects affected / exposed occurrences (all)	32 / 239 (13.39%) 39		
Nausea subjects affected / exposed occurrences (all)	53 / 239 (22.18%) 65		
Diarrhoea subjects affected / exposed occurrences (all)	52 / 239 (21.76%) 66		
Constipation subjects affected / exposed occurrences (all)	50 / 239 (20.92%) 50		
Dry mouth subjects affected / exposed occurrences (all)	14 / 239 (5.86%) 14		
Skin and subcutaneous tissue disorders			
Pruritus subjects affected / exposed occurrences (all)	26 / 239 (10.88%) 29		
Rash subjects affected / exposed occurrences (all)	20 / 239 (8.37%) 21		
Dry skin subjects affected / exposed occurrences (all)	12 / 239 (5.02%) 12		
Endocrine disorders			
Hypothyroidism subjects affected / exposed occurrences (all)	21 / 239 (8.79%) 22		
Musculoskeletal and connective tissue disorders			
Pain in extremity subjects affected / exposed occurrences (all)	15 / 239 (6.28%) 16		
Arthralgia subjects affected / exposed occurrences (all)	34 / 239 (14.23%) 38		

Back pain			
subjects affected / exposed	27 / 239 (11.30%)		
occurrences (all)	30		
Infections and infestations			
Urinary tract infection			
subjects affected / exposed	22 / 239 (9.21%)		
occurrences (all)	26		
Upper respiratory tract infection			
subjects affected / exposed	17 / 239 (7.11%)		
occurrences (all)	21		
Metabolism and nutrition disorders			
Hypokalaemia			
subjects affected / exposed	18 / 239 (7.53%)		
occurrences (all)	24		
Dehydration			
subjects affected / exposed	23 / 239 (9.62%)		
occurrences (all)	28		
Decreased appetite			
subjects affected / exposed	37 / 239 (15.48%)		
occurrences (all)	39		
Hyponatraemia			
subjects affected / exposed	15 / 239 (6.28%)		
occurrences (all)	17		
Hypophosphataemia			
subjects affected / exposed	12 / 239 (5.02%)		
occurrences (all)	14		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
12 January 2018	- Changes to primary endpoint - Statistical section updates - Adverse events updates
31 May 2018	Statistical section updates

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported